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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/741,106	12/21/2000	Michael A. Innis	12441.00003	7590

7590 08/18/2003

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 08/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/741,106	INNIS ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 21 July 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *14 and 15*.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-11,13,16-27,73 and 88*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Christopher S.F. Low

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Continuation Sheet (PTOL-303)

Continuation of 2. NOTE: The amendment to the claims does not resolve the current issues regarding obviousness type double patenting and under 35 USC 112, first and second paragraphs. In the amendment of July 21, 2003, claims 1 and 16 have been amended. Applicants' response has been fully considered, however, claims 1-11, 16-27 and 63 are rejected under the judicially created doctrine of obviousness-type double patenting, claims 1-11, 13, 16-27, 73 and 88 are rejected under 35 USC 112, first paragraph, and claims 2-13 are rejected under 35 USC 112, second paragraph.

If applicants' amendment were entered, it would have the following response:

1. Claims 1-11, 16-25 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U. S. Patent 6,174,721. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11, 16-25 and 73 in present application and claims 1-17 in the patent are obvious variations of a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI.

2. Claims 1-11, 16-27 and 73 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of U. S. Patent 5,589,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-11, 16-27 and 73 in present application and claims 1-24 in the patent are obvious variations of a chimeric protein comprising a Kunitz-type domain 1 of TFPI and a Kunitz-type domain 2 of TFPI-2; or a Kunitz-type domain 1of TFPI-2 and a Kunitz-type domain 2 of TFPI. In response, applicants indicate they will consider filing a Terminal Disclaimer upon indication of allowability of the pending claims. The comment is unpersuasive, and the ground of rejection remains. No allowable material can be indicated when a ground of rejection remains.

3. Claims 1-11, 13, 16-27, 73 and 88 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or, a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFP or a mutein thereof, where the substitution in the mutein is defined (see page 8, line 19-page 9, line 3; page 10, line 5-12), does not reasonably provide enablement for a chimeric protein comprising a Kunitz-type domain 1 of TFPI or a mutein thereof and a Kunitz-type domain 2 of TFPI-2 or a mutein thereof; or, a Kunitz-type domain 1 of TFPI-2 or a mutein thereof and a Kunitz-type domain 2 of TFP or a mutein thereof, wherein the chimeric protein binds and inhibits factor VIIa/tissue factor complex and binds to and inhibits factor Xa, however, the mutation in the mutein is not defined. The specification indicates muteins have 1-5 amino acid substitutions in the wild-type sequence and describes certain substitutions in the muteins (e.g., the substitution at the P1 reactive site and substitutions at positions within 5 amino acids of the P1 reactive sites in Kunitz-type domains; page 7, line 26-page 8, line 3; page 8, line 19-page 9, line 21), however, the specification does not identify most substitutions in the TFPI or TFPI-2, nor demonstrates the effect of the substitution on the affinity for factor VIIa/TF and factor Xa. Moreover, there are no working examples indicating various muteins except for the substitution at P1 reactive site of Kunitz-type domains, e.g., SEQ ID NO:9. Furthermore, the specification has not demonstrated various muteins of Kunitz-type domain 1 or 2 of TFPI or TFPI-2 have inhibitory activity against factor VIIa/TF and factor Xa. Since the specification fails to provide sufficient teachings on identities of various muteins and the inhibitory effects of the muteins, it is necessary to have additional guidance on the muteins and to carry out further experimentation to make/use chimeric proteins containing the muteins, and assess the inhibitory effects to Factor VIIa/TF and factor Xa. In response, applicants indicate "mutein" has been defined in the specification, and the specificaiton teaches numerous examples of such muteins of TFPI and TFP-2, and these teachings bear a reasonable correlation to the scope of the recited muteins of Kunitz-type domains 1 and 2 of TFPI and TFPI-1; and claim 1 has been amended to include "the chimeric protein binds and inhibits factor VIIa/tissue factor complex and binds to and inhibits factor Xa", which excludes muteins that would render the claimed proteins non-functional; and three references regarding assaying the inhibition of factor VIIa/TF and factor Xa (Hamamoto et al., J. Biol. Chem. 268, 8704-8710 (1993); Huang et al. J. Biol. Chem. 268, 16950-26955 (1993); Sprecher et al., PNAS 91, 3353-3357 (1994)) have been provided by applicants to identify muteins of the recited Kunitz domains that fall within the scope of the claim (pages 10-12 of the response). The response has been fully considered, however, the argument is found persuasive because the claim only recites the function of the muteins in the chimeric protein, but it does not have structural definition of the mutein, even though the specification has described certain substitution in the muteins, they are not cited in the claim. Without structural description of the muteins, one skilled in the art would not know how to identify a functional mutein.

4. Claims 2-13 are rejected under 35 USC 112, second paragraph because of the use of the term "wherein a, b are integers from 0-6". The term "wherein a, b are integers from 0-6" renders the claim indefinite, it is unclear how a compound having a generic formula A-(X1)a-B-(X2)b-C with a=0 or b=0 can be a chimeric protein comprising a Kunitz domain of TFPI-2 and a Kunitz domain of TFPI? Claims 3-13 are included in the rejection because they are dependent on a rejected claim and do not correct the deficiency of the claim from which they depend. In response, applicants indicate the chimeric protein in claim 1 recites two Kunitz domains, and claims 2-13 are dependent from claim 1, thus the chimeric protein in claims 2-13 precludes the combination a=b=0 (pages 12-13 of the response). The argument is not persuasive, because claims 2-13 recites the chimeric protein can have a structure of a or b being 0, which does not conform the limitation set forth in claim 1.

Continuation of 5. does NOT place the application in condition for allowance because: The amendment to the claims does not resolve current issue on obviousness-type double patenting and under 35 USC 112, first and second paragraphs. .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (703) 308-9437. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, Ph. D. can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D.
August 17, 2003